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1 384 523

PATENT SPECIFICATION (11) 1 384 523

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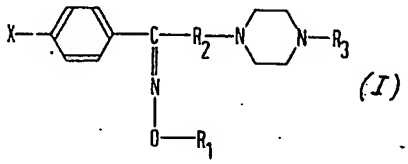
(19)

(54) NEW OXIME DERIVATIVES AND THEIR PREPARATION

(71) We, ANDRE BUZAS, a French citizen of 25 Rue Mignote, Bievres, Essonne, France, and Les Laboratoires Bruneau et Cie, a French Body Corporate of 17 Rue de Berri, Paris, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to oxime derivatives of pharmaceutical utility and their preparation. It is an improvement in, or modification of, the invention of our Application No. 56116/72.

In our Application No. 56116/72, we have described and claimed the compounds of the formula



(I)

in which X represents a halogen atom, preferably chlorine or fluorine, R_1 represents a lower aliphatic hydrocarbyl group, a lower aliphatic hydrocarbyl group substituted by a tertiary amino radical, an alkyl - carbonyl, an aralkyl - carbonyl, an aralkenyl-carbonyl, a phenyl - carbonyl, a furyl - carbonyl or a pyridyl - carbonyl radical, optionally substituted by up to three radicals chosen from halogen atoms and alkyl and alkoxy radicals, the said alkyl and alkenyl radicals each containing a maximum of 8 carbon atoms, R_2 represents a linear or branched aliphatic hydrocarbyl group of 1 to 3 carbon atoms, and R_3 represents an arylaliphatic or aromatic hydrocarbyl group, and their pharmaceutically acceptable acid addition salts.

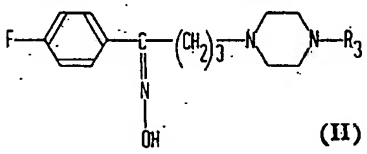
The term "lower aliphatic" as used herein refers to the groups having up to 6 carbon atoms.

These compounds are of low toxicity and have pharmacological activity, especially as analgesic agents, anti-inflammatory agents and musculotropic spasmolytic agents.

It has now been found that compounds of the aforesaid formula in which X is fluorine, R_1 is allyl, β - diethylamino - ethyl, β-morpholino - ethyl, 3,4,5 - trimethoxy - benzoyl or 2 - chloro - nicotinoyl, R_2 is $-(CH_2)_3-$, and R_3 is 2 - pyridyl or 2-pyrimidinyl, and their pharmaceutically acceptable acid addition salts, also have valuable properties as analgesic agents, and as anti-inflammatory and musculotropic spasmolytic agents, combined with low toxicity.

Suitable salts are, especially, the hydrochlorides and maleates. Such salts may be made by reaction of the bases with a pharmaceutically acceptable organic acid such as citric, maleic or methane - sulphonic acid, or inorganic acid such as hydrochloric, nitric or sulphuric acid. They are crystalline products which are stable and soluble in water.

The compounds of the present invention may be prepared by the same process as that described in the main patent, i.e. by reaction of an oxime of the formula:



(II)

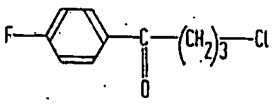
in which R_2 is as hereinbefore defined, with a compound of the formula

$$Hal—R_1$$

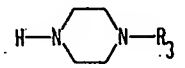
wherein Hal represents halogen, preferably chlorine, and R_1 is as hereinbefore defined.

When R_1 is allyl, β - diethylaminoethyl, or β - morpholino - ethyl, the oxime can be employed in the form of its sodium or potassium salt and the reaction can be carried out in an alcoholic diluent such as ethanol or tertiary butyl alcohol. When R_1 is 3,4,5-trimethoxybenzoyl or 2 - chloro - nicotinoyl, the reaction can be carried out in a diluent such as pyridine and the hydrohalide (e.g. hydrochloride) of the product base is then obtained directly.

The oximes of formula II are new compounds. They can be obtained by the reaction, in known manner, of hydroxylamine, in the form of its hydrochloride, and the corresponding ketone, preferably in an aqueous-alcoholic medium, where necessary in the presence of sodium hydroxide. The ketone, in its turn, can be prepared by reaction of the chlorinated ketone of formula:



with a piperazine of formula:



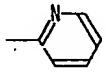
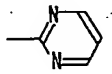
preferably in an organic diluent such as benzene, toluene or chloroform.

The following Examples illustrate the invention. Examples I and II illustrate the preparation of the starting oximes and Examples 1 to 8 the preparation of the compounds of formula I. The characteristics of the two starting oximes are given in Table I and those of the compounds of formula I in Table II.

EXAMPLES I and II.

The starting oximes used to prepare the compounds of the present addition are prepared in accordance with Method A described in Example I of the main patent.

TABLE I

Oxime No.	X	R_2	R_3	Melting point (°C) (Köfler)
I	F	$-(CH_2)_3$		160
II	F	$-(CH_2)_3$		128

EXAMPLE 1.

1 - [(3,4,5 - Trimethoxy - benzoyloxy)-imino] - 1 - (4 - fluoro - phenyl) - 4 - [4 - (2 - pyridyl) - 1 - piperazinyl]-butane hydrochloride (Compound No 4)

A solution of 27.5 g (0.12 mol) of 3,4,5-trimethoxy - benzoyl chloride in 100 ml of dry methylene chloride is added slowly and with stirring to a suspension of 34.2 g (0.1 mol) of oxime I in 150 ml of dry methylene chloride, kept at 0°C. At the end of the addition, the mixture is allowed to return to ambient temperature and stirring is continued for 8 hours. The precipitate is filtered off and washed with methylene chloride and then recrystallised from a mixture of methanol and ethanol (1:5). 44 g (yield 82%) of white crystals, m.p. 210°C (Köfler) with decomposition, are obtained.

EXAMPLE 2.

1 - [(2 - Morpholino - ethoxy) - imino]-1 - (4 - fluorophenyl) - 4 - [- (2-pyrimidinyl) - 1 - piperazinyl]-butane dimaleate (Compound No. 6)

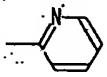
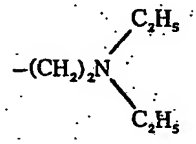
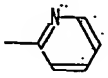
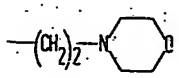
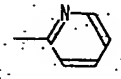
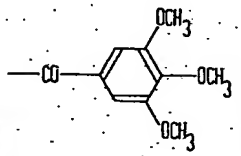
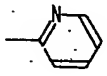
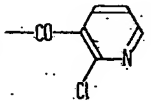
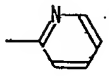
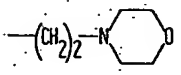
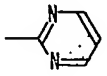
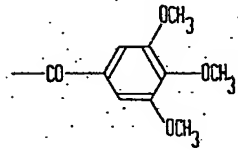
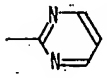
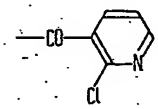
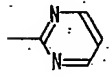
37.95 g (0.1 mol) of the hydrochloride of oxime II are added with stirring to a boiling solution of 22.44 g (0.2 mol) of

potassium tert - butylate in 500 ml of tert-butyl alcohol. The mixture is heated under reflux for 2 hours and 14.95 g (0.1 mol) of 2 - morpholino - ethyl chloride are then added. The mixture is again heated under reflux for 1 hour. After cooling, the solvent is removed under reduced pressure and the residue is taken up in water and extracted with diethyl ether. The ether solution is washed with water and dried over sodium sulphate. The ether is removed under reduced pressure, and the oily residue is dissolved in 200 ml of absolute ethanol. 35 g of maleic acid are added and the mixture is brought to the reflux temperature. After cooling, the crystals which have separated out are filtered off. 53.3 g (yield 77%) of white crystals, m.p. 162°C (Köfler) are obtained.

EXAMPLES 3 to 8.

Working under the same conditions as in Examples 1 and 2, the compounds which are given in Table II are obtained.

TABLE II

Compound No.	X	R_1	R_2	R_3	Salt prepared	Melting point (°C)
1	F	$-CH_2-CH=CH_2$	$-(CH_2)_3-$		maleate (di)	140
2	F		$-(CH_2)_3-$		maleate (tri)	132
3	F		$-(CH_2)_3-$		maleate (tri)	144
4	F		$-(CH_2)_3-$		hydrochloride (mono)	210
5	F		$-(CH_2)_3-$		hydrochloride (mono)	210
6	F		$-(CH_2)_3-$		maleate (di)	162
7	F		$-(CH_2)_3-$		hydrochloride (mono)	215
8	F		$-(CH_2)_3-$		hydrochloride (mono)	185

Compounds 1 to 8 have been pharmacologically investigated, employing the following tests:

Acute toxicity (LD_{50}) in mice after oral administration, with determination of a toxicity limit or calculation of the 50% lethal dose according to BEHRENS and KARBER (Arch. exp. Pathol., Pharmakol., 1935, *177*, 379);

Actimetry, by the method of BOISSIER (Arch. int. Pharmacodyn., 1961, *158*, 212) in mice treated by oral administration;

Anti-convulsant activity, in relation to maximum electric shock (MES) and intoxication induced by pentetrazole (PTZ);

Traction test by the method of BOISSIER (Thérapie, 1958, *13*, 1074) in mice treated by oral administration;

Potentiation of barbiturate-induced narcosis in mice (compounds administered orally 45 minutes before the liminal (subthreshold) dose of sodium mebubarbital, 25 mg/kg, administered intraperitoneally), the activity being assessed on a scale of from 0 to 3 crosses.

Painful abdominal cramp test, induced in mice by injection of phenylbenzoquinone, by the method of HENDERSHOT and FORSAITH (J. Pharmacol, exp. Therap., 1959, *125*, 237), the compounds being administered orally 30 minutes before phenylbenzoquinone and the 50% effective dose being determined;

Sub-planter oedema test, induced in rats by injection of carragenine by the method of WINTER (Proc. exp. Biol. Med., 1962, *3*, 515), the activity of the various compounds administered orally being compared with that of phenylbutazone;

Guinea pig's ileum stimulated *in vitro* by histamine (Hi) or by barium chloride (Ba). Guinea pig's seminal vesicles stimulated by adrenalin (Ad). The 50% effective doses are expressed in μg/ml.

The results obtained are given in Table III.

TABLE III

Compound No.	LD_{50} mg/kg administered orally	MES ED_{50} mg/kg administered orally	PTZ ED_{50} mg/kg administered orally	Actimetry ED_{50} mg/kg administered orally	Traction ED_{50} mg/kg administered orally	Potentiation of Narcosis. (Activity from 0 to +++)	Cramp induced by phenylbenzoquinone ED_{50} mg/kg administered orally	Carragenine (Activity relative to phenylbutazone = 1)	Hi ED_{50} µg/ml	Ba ED_{50} µg/ml	Ad ED_{50} µg/ml
1	1,200	>400	>400	40	200	+++	50	0	0.5	50	0.5
2	1,200	>400	>400	50	>200	++	30	0	>0.5	5	0.5
3	1,200	>400	>400	90	>200	+++	50	0.3	>0.5	50	0.5
4	>1,600	>400	>400	50	>200	+++	90	0.5	—	—	—
5	600	>400	>400	50	200	+++	110	0.5	>0.5	5	0.5
6	300	>200	>200	100	>200	+++	100	0.3	>0.5	>50	5
7	1,600	>400	>400	100	>200	+++	100	0	>0.5	>50	>5
8	1,200	>400	>400	40	>200	++	40	0.1	>0.5	50	5

It is apparent from this Table that the majority of the compounds investigated are relatively non-toxic (LD_{50} greater than 1 g/kg); all the compounds investigated possess analgesic properties, particularly compounds 2 and 8; the compounds possess both antihistaminic and psychotropic properties.

Because of these properties given above, the compounds of formula I can be used in human and veterinary medicine, particularly as analgesics, and also as psychosedatives, anti-inflammatory, anti-allergic, anti-spasmodic and peripheral vasodilating agents.

The invention also provides a pharmaceutical composition comprising, in association with a compatible pharmaceutical carrier, a compound of the invention as base or pharmaceutically acceptable acid addition salt.

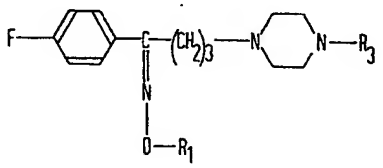
The compounds of the present invention can then be administered as gelatine-coated capsules, pills, tablets or sterile injectable solutions.

A single dose, e.g. tablet or gelatine-coated pill, can contain from 20 to 200 mg of active principle. An injectable solution of 1 to 5 ml can contain from 10 to 100 mg of active principle.

The usual oral daily dose is from 50 to 200 mg. for an adult.

WHAT WE CLAIM IS:—

1. A compound of the formula:

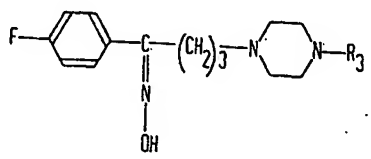


in which R_1 is allyl, β - diethylamino - ethyl, β - morpholino - ethyl, 3,4,5 - trimethoxy - benzoyl or 2 - chloro - nicotinoyl and R_3 is 2 - pyridyl or 2 - pyrimidinyl and its pharmaceutically acceptable acid addition salts.

2. 1 - [(2 - Diethylamino - ethoxy) - imino] - 1 - (4 - fluorophenyl) - 4 - [4-(2 - pyridyl) - 1 - piperazinyl] - butane, and its pharmaceutically acceptable acid addition salts.

3. 1 - [(2 - chloro - nicotinoyloxy) - imino] - 1 - (4 - fluorophenyl) - 4 - [4 - (2 - pyrimidinyl) - 1 - piperazinyl]-butane and its pharmaceutically acceptable acid addition salts.

4. A process for the preparation of a compound as claimed in claim 1, which comprises reacting an oxime of the formula:



in which R_3 is as defined in claim 1, with a compound of the formula:

$$Hal—R_1$$

in which Hal represents halogen and R_1 is as defined in claim 1.

5. Process according to claim 4, in which R_1 is allyl, β - diethylamino - ethyl, or β-morpholino - ethyl, the oxime is employed as its sodium or potassium salt, and the reaction is carried out in an alcoholic diluent.

6. Process according to claim 4, in which R_1 is 3,4,5 - trimethoxybenzoyl or 2-chloronicotinoyl, the reaction is carried out in a diluent, and the hydrochloride of the produced base is obtained directly.

7. Process according to any of claims 4 to 6 in which Hal represents chlorine.

8. A process according to claim 5 substantially as described in Example 2.

9. A process according to claim 6 substantially as described in Example 1.

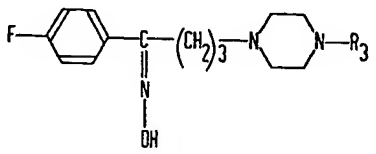
10. A compound as claimed in claim 1 when prepared by the process of any of claims 4 to 9.

11. A pharmaceutical composition comprising, in association with a compatible pharmaceutical carrier, a compound as claimed in any of claims 1 to 3 or 10 as base or pharmaceutically acceptable acid addition salt.

12. A composition according to claim 11 in the form of a tablet, pill or capsule.

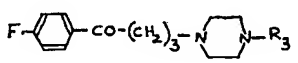
13. A composition according to claim 11 in the form of a sterile injectable solution.

14. An oxime of the formula:



in which R_3 is 2-pyridyl or 2-pyrimidinyl.

15. Process for the preparation of an oxime as claimed in claim 14, which comprises reacting hydroxylamine hydrochloride with a ketone of the formula:



in which R_3 is 2-pyridyl or 2-pyrimidinyl.

16. Process according to claim 15 in which the reaction is carried out in an aqueous-alcoholic medium.

17. Process according to claim 15 or 16 in which the reaction is carried out in the presence of sodium hydroxide.

18. An oxime as claimed in claim 14 when prepared by the process of any of claims 15 to 17.

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